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Newer Antiarrhythmic Drugs

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SLEISENGER:* *The topic of this conference is newer antiarrhythmic drugs and our discussant is Dr. David Hess.*

DR. HESS:† The need for newer antiarrhythmic drugs has never been more apparent. For decades physicians have sought an antiarrhythmic agent that had an extended half-life, a minimum of side effects and excellent clinical effectiveness, but such an ideal antiarrhythmic drug is not yet available.

In cardiac care newer antiarrhythmic agents are required for two general clinical uses. First, they are needed in the treatment of supraventricular tachycardia. The management of supraventricular tachyarrhythmias has improved with the introduction of β-adrenergic blocking agents. However, both propranolol and digoxin may be ineffective in controlling supraventricular arrhythmias in situations such as episodes of paroxysmal supraventricular tachycardia (PSVT), atrial fibrillation and atrial flutter in patients with chronic lung disease or congestive heart failure. Hence, nontoxic, effective antiarrhythmic drugs are needed to manage these conditions appropriately.

Second, newer antiarrhythmic drugs are needed for the treatment of ventricular arrhythmias. The comprehensive evaluation and treatment of atherosclerotic coronary artery disease in the 1970's resulted in the development of paramedically manned mobile cardiac units and widespread instruction in cardiopulmonary resuscitation. These factors are now responsible for a significant number of patients surviving out-of-hospital cardiac arrest. However, because there is a high incidence of recurrence of cardiac arrest in this group of patients,[1-3] physicians have learned that aggressive management of these arrhythmias is required. In addition, findings of epidemiologic studies carried out in the 1970's indicate that patients are at a higher risk for sudden cardiac death if they have survived acute myocardial infarction and demonstrate certain premature ventricular depolarization (PVD) patterns during ambulatory monitoring.[4,5] Although it has not been proved conclusively that suppression of arrhythmias will prevent sudden death, it appears prudent to institute therapy with antiarrhythmic drugs in these patients. However, quinidine, procainamide and disopyramide are not always effective in controlling these ventricular arrhythmias and often are associated with significant side effects. Thus, newer antiarrhythmics are needed to supplement the treatment of arrhythmias in these patients with coronary artery disease.

In reviewing the world literature, one notes that there are some 20 antiarrhythmic drugs that are available in other parts of the world but which are not readily accessible in the United States. About ten of these agents are available on experi-

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ABBREVIATIONS USED IN TEXT

AV = atrioventricular
PSVT = paroxysmal supraventricular tachycardia
PVD = premature ventricular depolarization
SA = sinoatrial
SVT = supraventricular tachycardia

mental protocols, and four of the most promising medications are discussed here in detail. For completeness, other experimental antiarrhythmic drugs are included in Tables 1 through 3 but will not be reviewed in the text.

Verapamil

Verapamil is a papaverine derivative that was first developed in West Germany in 1962. Initially, it was used as an antianginal agent in Western European countries. However, not long after its release, verapamil was found to have unique electrophysiological properties and proved very effective in treating a variety of supraventricular arrhythmias.

To understand verapamil's antiarrhythmic actions, the cardiac cellular transmembrane potential will be reviewed. The fast response action potential (Figure 1A) is found in the peripheral nerves, in skeletal muscle and within the heart. This action potential is dependent on rapid sodium influx across the channels in the cellular

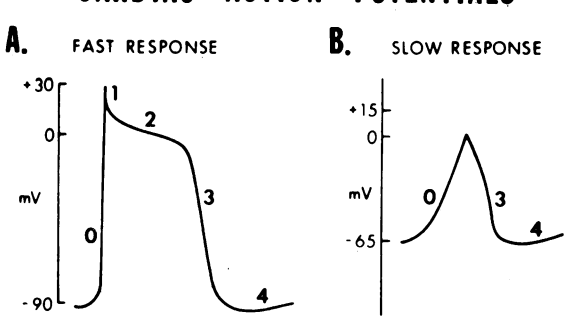

Figure 1.—A. Cellular transmembrane potential of a fast response cell. The action potential is characterized by its rapid upstroke (0), overshoot (1), plateau phase (2), repolarization (3) and slow diastolic depolarization (4). **B.** Cellular transmembrane potential of a slow response cell, characterized by slow upstroke (0), repolarization (3) and diastolic depolarization (4).

TABLE 1.—*Electrophysiological Characteristics of Seven Experimental Antiarrhythmic Drugs in Animal Studies**†*

Drug	*APA*	*APD*	*dV/dt*	*MDP*	*ERP*	*Cond Vel*	*Normal Phase 4*	*Memb Resp*	*ET*	*VFT*	*Contractility*	*Ca^{++} Current*
Verapamil	0	↓	0	0	0	0	↓	0	..	0	↓	Inhibit
Encainide	0	↓	↓	0	↑	↓	↓	..	0	?	0↓	0
Tocainide	0	↓	0↓	0	↓	↓	↓	↓	↑	↑	..	0
Amiodarone ..	0	↑	0↓	0	↑	↓	0	↓	..	..	↓	..
Aprindine	0	↓	↓	0	↓	↓	↓	↓	↑	↑	↓	0
Ethmozin	↓	↓	↓	0↓	↓	↓	0	↓	↑	0	↑then↓	0
Mexilitine	0	↓	↓	0	↓	↓	↓	↓	↑	↑	↓	0

↑ = increase; ↓ = decrease; 0 = no change; 0↑ or 0↓ = slight increase or slight decrease, respectively; APA = action potential amplitude; APD = action potential duration; Ca^{++} current = slow current or slow response; Cond Vel = conduction velocity; dV/dt = rate of rise upstroke (phase 0) of action potential; ERP = effective refractory period; ET = excitability threshold; MDP = maximal diastolic potential; VFT = ventricular fibrillation threshold

*Results presented may vary according to tissue type, experimental conditions and drug concentration. Animal data are from "fast-response" type fibers.
†Adapted from Zipes and Troup.[17]

TABLE 2.—*Electrophysiological Characteristics of Seven Experimental Antiarrhythmic Drugs in Human Studies**†*

Drug	*Sinus Rate*	*PR*	*QRS*	*QT*	*A-H*	*H-V*	*ERP-AVN*	*ERP-HPS*	*ERP-A*	*ERP-V*
Verapamil	↓	↑	0	0	↑	0	↑	0	0	0
Encainide	0	↑	↑	↑	0	↑	0	↑	0	0
Tocainide	0↓	0	0	0↓	0↑	0	↓	..	↓	↓
Amiodarone ..	↓	↑	↑	↑	↑	0	↑	↑	↑	↑
Aprindine	↓	↑	↑	0↑	↑	..	↑	↑	↑	↑
Ethmozin	0↓	0↑	0↑	0	..	..	..	..	..	..
Mexilitine ...	0	0	0	0	0↑	0↑	0↑	0↑	0	0

↑ = increase; ↓ = decrease; 0 = no change; 0↑ or 0↓ = slight increase or slight decrease, respectively; A = atrium; AVN = atrioventricular node; ERP = effective refractory period; HPS = His-Purkinje system, V = ventricle

*Results presented may vary according to tissue type, experimental conditions and drug concentration.
†Adapted from Zipes and Troup.[17]

TABLE 3.—*Clinical Characteristics of Seven Experimental Antiarrhythmic Drugs**

Drug	*Intravenous*	*Oral*	*Effective Serum or Plasma Concentration (μg/ml)*	*Elimination Half-Life (hr)*	*Absorption*	*Metabolic Secretion Route*	*Side Effects*	*Onset of Action*	
								Intravenous (min)	*Oral (hr)*
Verapamil	0.075-0.15 mg/kg	Maintenance: 80-120 mg q 8 hr or q 6 hr	..	3-7	Good	Hepatic	Neurologic Gastrointestinal Cardiovascular	<5	1-2
Tocainide	0.5-0.75 mg/kg/min for 15 min	Loading: 400-600 mg Maintenance: 400-800 mg q 8 hr	3.5-10	10-17	Good	Renal 40% Probably hepatic 60%	Neurologic Gastrointestinal Cardiovascular	5-10	1-1/2
Encainide	0.9 mg/kg over 15 min	25-75 mg q 6 hr	2-56 ng/ml	3.4	Good	Hepatic	Tinnitus Headache Dizziness	5-10	1-2
Amiodarone ..	5-10 mg/kg	Maintenance: 200-800 mg	..	..	Fair	..	Ophthalmologic Endocrine Neurologic Dermatologic Cardiovascular	5-10	4-6
Aprindine	200 mg at 2 mg/min; 30 min later 100 mg at 2 mg/min; 6 hr later, 100 mg at 2 mg/min	Loading: 100 mg q 6 hr, day 1 75 mg q 6 hr, day 2 50 mg q 6 hr, day 3 Maintenance: 25-50 mg q 8 hr or q 12 hr	1-3	20-30	Good	Hepatic	Neurologic Gastrointestinal Hematologic Cardiovascular	5-10	2
Ethmozin	Loading: 1-3 mg/kg†	Maintenance: 75-150 mg q 6 hr‡	0.5-1.0	5-10‡	Good	Probably hepatic†	Neurologic Gastrointestinal Cardiovascular	<5†	2†
Mexilitine	Loading: 1,200 mg/12 hr; Maintenance: 250-500 mg/12 hr	Loading: 400-600 mg Maintenance: 200-300 mg q 8 hr	0.5-2.0	10-26	Good	Probably hepatic	Neurologic Gastrointestinal Cardiovascular	<5	1-2

q = every

*Adapted from Zipes and Troup.[17]

†Animal data.

‡According to studies in progress, maintenance doses may be in the range of 250 mg every 8 hours and provide a slightly longer half-life.

membrane. The potential is characterized by a rapid upstroke, overshoot and plateau phase before repolarization. This particular type of action potential occurs in atrial and ventricular muscle and in the cells of the His-Purkinje system. However, the sinoatrial (SA) node and the atrioventricular (AV) node do not have fast response action potentials when studied by microelectrode techniques. Instead, they have an action potential depicted in Figure 1B—a slow response action potential. This action potential differs from the fast response in that the depolarization demonstrates a slowed upstroke and absence of an overshoot and plateau phase. Experimental models have shown that a slow influx of calcium ions (and perhaps sodium ions) is responsible for generating this action potential. These ionic calcium currents are blocked by verapamil.[6] Because the AV and SA nodes depend on the slow response action potential for excitation and conduction, medications that specifically inhibit calcium transport will increase the refractoriness and decrease the conduction velocity of these tissues. These electrophysiological properties of verapamil form the basis for its antiarrhythmic action (Tables 1 and 2).

The clinical pharmacology of verapamil is outlined in Table 3. Briefly, it is rapidly and completely absorbed from the gastrointestinal tract, excreted by way of hepatic metabolism and has a half-life of approximately six hours. The hemodynamic effects of verapamil on normal volunteers have been examined in several studies.[6,7] Normal subjects exhibit a primary decrease in systemic vascular resistance and a compensatory increase in heart rate and cardiac output. The left ventricular end-diastolic pressure does not change in these volunteers after verapamil administration. In patients with congestive heart failure, verapamil has two primary opposing effects.[8] By decreasing systemic vascular resistance it may increase cardiac output without a change in heart rate. This "afterload reduction" effect of verapamil, however, can be cancelled by the drug's direct negative inotropic effect on the myocardium. Hence, hemodynamic changes in patients with left ventricular dysfunction may be variable after verapamil administration.

Because verapamil inhibits the slow calcium currents, there is a preferential effect on the SA and AV nodes. Thus, verapamil is most effective clinically in treating arrhythmias that involve the SA and AV node. For example, patients with atrial fibrillation or atrial flutter with rapid ventricular response are excellent candidates for verapamil therapy because the drug slows conduction in the AV node. Verapamil is effective in AV nodal reentrant tachycardia for the same reasons. The effectiveness of verapamil in treating supraventricular arrhythmias has been evaluated by numerous studies in Western Europe and South America; the following review is a composite of 134 clinical studies of this drug.[9]

In assessing verapamil's effectiveness in supraventricular tachycardia (SVT), the above studies usually included patients presenting with a narrow complex tachyarrhythmia, but who had no underlying organic heart disease. Most of these patients had either AV nodal reentrant tachycardia or tachycardia involving an AV bypass tract (Wolff-Parkinson-White syndrome). A total of 1,607 patients with paroxysmal SVT were treated with verapamil given intravenously.[9] In 81 percent of the patients conversion to normal sinus rhythm occurred after the administration of a 10-mg intravenous bolus of the drug. An additional 9 percent of patients were judged to have a good clinical response because of a significant reduction in the SVT rate. Overall, approximately 90 percent of patients responded to this mode of treatment. This remarkable response has not been previously documented with any of the antiarrhythmic drugs now available in the United States.

Verapamil's effectiveness in controlling atrial fibrillation with a rapid ventricular response rate was assessed in 65 clinical studies.[9] The drug was given as an intravenous injection (10 to 20 mg) to 1,474 patients and in 16 percent conversion to normal sinus rhythm occurred. However, the important finding was a significant reduction in the ventricular response rate in 78 percent of the patients. A significant rate reduction was defined as a 30 percent decrease in the ventricular response or a reduction in rate to less than 100 beats per minute. In total, 94 percent of patients with atrial fibrillation responded to the intravenous administration of verapamil. The clinical results of treating patients with atrial flutter have been similar—85 percent of the patients treated had either a significant reduction in ventricular rate or conversion to normal sinus rhythm.[9] The response of these two types of atrial arrhythmias is especially important because digoxin is ineffective in many patients and propranolol is con-

traindicated in those with chronic lung disease or congestive heart failure. Hence, the addition of a safe, rapid-acting antiarrhythmic agent that reduces the ventricular response rate is an important addition to drugs now available.

Although digoxin and propranolol therapy and cardioversion are often effective in treating patients with atrial fibrillation or atrial flutter and rapid ventricular response, verapamil's rapid effectiveness in these same patients provides clinicians with an added dimension in treating certain subgroups of patients. For example, Hagemeijer[10] studied 16 patients with acute myocardial infarction who had either atrial fibrillation or atrial flutter with a rapid ventricular response. These patients had no clinical evidence of congestive heart failure, and the arrhythmias occurred within the first 72 hours of infarction. The arrhythmias were treated with titrated doses of intravenously given verapamil (average dose 10 mg) over a ten-minute interval. Eight patients had atrial fibrillation with an average ventricular rate of 160 beats per minute before treatment. Ten minutes after the administration of verapamil, the average ventricular rate was approximately 100 beats per minute. By inhibiting slow-current calcium channels, verapamil increased the refractoriness of the AV node and resulted in a decrease in the ventricular response rate in these patients. Atrial flutter with an average ventricular rate of 150 beats per minute was present in an additional eight patients. After treatment with verapamil, conversion to normal sinus rhythm occurred in seven patients, and in the eighth patient, a reduction in ventricular rate from 154 to 75 beats per minute occurred. Clearly, in the case of acute myocardial infarction, verapamil represents a significant therapeutic agent capable of rapidly reducing the ventricular response rate in patients with atrial fibrillation or atrial flutter. This effect could be beneficial in preserving ischemic myocardium or in relieving rate-related angina or heart failure. Hagemeijer's results require further investigation before verapamil can be recommended for treating acute myocardial infarction, but its potential usefulness cannot be ignored.

The Division of Cardiology at the University of California, San Francisco (UCSF) has used verapamil in the treatment of approximately 50 patients with supraventricular tachyarrhythmias. Our results using intravenous verapamil therapy have been similar to those of the studies outlined above; that is, approximately 85 percent to 90 percent had an excellent initial response.[11] In addition, long-term oral verapamil therapy has been evaluated in 18 patients followed for a mean of 16 months. Although verapamil produced objective and subjective improvement in the patients' supraventricular arrhythmias, 15 of the 18 patients required concomitant administration of either digoxin or another conventional antiarrhythmic drug to obtain the desired clinical response. The patients tolerated the on-going oral verapamil therapy without significant side effects, demonstrating that long-term treatment is both effective and nontoxic.

As with any drug, a clinician must weight the risk-benefit ratio before initiating treatment. Fortunately, verapamil has very low toxicity. A review of 8,072 patients treated with the drug, either intravenously or orally on a long-term basis, shows an overall incidence of side effects of 8 percent.[9] However, only 1 percent to 2 percent (73 patients) of the patients treated had to discontinue the drug because of intolerable side effects. The most common side effects (Table 4) were gastrointestinal, including nausea, vomiting and constipation.

Some patients, especially those predisposed to migraine, may have headaches. Whether these

TABLE 4.—*Common Side Effects of Verapamil and Amiodarone Therapy*

	Side Effects				
Drug	*Gastrointestinal*	*Central Nervous System*	*Integument*	*Endocrine*	*Cardiovascular*
Verapamil	Nausea Vomiting Constipation	Dizziness Vertigo Headache	Pruritis Rash Flushing	.....	Bradycardia Hypotension Congestive heart failure AV dissociation or block
Amiodarone	Nausea Constipation	Motor neuropathy Tremor Cerebellar ataxia	Corneal microdeposits Dermatitis Blueing of the skin	Hypothyroidism Hyperthyroidism	Bradycardia Hypotension AV nodal block

AV = atrioventricular

headaches are related to extracranial vascular smooth muscle relaxation is unknown.

Cardiovascular side effects are secondary to verapamil's effect on automaticity, conduction and contractility. Because it depresses phase 4 depolarization in the sinus node, verapamil can cause deterioration in sinus node function in patients with sick sinus syndrome. Because it decreases conduction through the AV node, verapamil can precipitate AV block. The negative inotropic properties of verapamil can result in congestive heart failure in patients with underlying left ventricular dysfunction, especially if given in conjunction with propranolol or disopyramide.

What does the future hold for verapamil as an antiarrhythmic agent? Once verapamil is approved by the Food and Drug Administration and clinical experience in the United States accumulates, verapamil will probably become the drug of choice for the short-term treatment of PSVT. It will probably become an adjunct to digoxin in controlling the ventricular response rate in patients with atrial fibrillation and atrial flutter, especially in patients with chronic lung disease. In addition, verapamil will be a useful adjunct in the long-term treatment of recurrent PSVT. At present, there are insufficient clinical data to support a role for verapamil in the treatment of ventricular tachycardia.

Encainide

In contrast to verapamil, encainide is an antiarrhythmic agent developed by the Mead Johnson Laboratories for specific use in the treatment of ventricular arrhythmias. Encainide is a unique agent, which combines the electrophysiological effects of lidocaine and quinidine (Tables 1 and 2).[12,13] At the cellular level, encainide shortens the duration of the action potential (an effect of lidocaine) and depresses the rate of rise of the action potential upstroke (an effect of quinidine); that is, encainide slows conduction in ventricular and His-Purkinje tissues. Encainide also increases the effective refractory period and decreases ventricular excitability (both effects of quinidine).

In contrast to quinidine, encainide has no consistent effect on the peripheral vasculature, and, hence, alterations in blood pressure are uncommon. The atrial muscle, AV node and sinus node are unaffected by the rapid administration of encainide intravenously.[12,13] However, the effects of long-term oral encainide treatment on these tissues have not been completely assessed. Thus, encainide combines the desirable ventricular antiarrhythmic characteristics of lidocaine and quinidine therapy without compounding unwanted side effects.

The clinical pharmacology of encainide is outlined in Table 3. The drug is rapidly absorbed after oral administration, is metabolized in the liver and has a half-life of approximately two hours. Despite its relatively short half-life, encainide can usually be administered every six hours. This is the result of the wide margin between drug plasma concentrations that suppress the arrhythmia and those that produce side effects. In addition, encainide may have active metabolites. Encainide does not produce significant changes in cardiovascular dynamics in normal volunteers.[14] To date, there is no comprehensive information available on the hemodynamic effects of encainide in patients with congestive heart failure.

Because encainide's development is recent, only a few clinical trials are available for review. Two of these, however, warrant in-depth analysis. Roden and colleagues[15] carried out studies in 11 patients without organic heart disease. The patients had no symptoms of angina, no conduction disturbances on the electrocardiogram and no evidence of heart failure (average ejection fraction by radionuclide ventriculography was 63 percent). The common denominator for the study group was a high frequency of ventricular arrhythmias. An average of 771 PVD's per hour were recorded during the placebo phase of the study. During encainide therapy, 10 of the 11 patients had virtually total suppression of PVD's; that is, the PVD frequency during drug therapy was 0.4 percent of the frequency during placebo. Hence, encainide was dramatically effective in suppressing premature ventricular depolarizations. The limitation of Roden's study is in its patient population. Clinicians are more interested in PVD suppression in patients with organic heart disease. It is in this group that complex PVD patterns may be harbingers of sudden death. Hence, total suppression of PVD's in these patients could lead to prevention of death from arrhythmias.

The evaluation of encainide in patients with organic heart disease is underway, and one clinical abstract is available for review. Mason and coworkers[16] evaluated encainide in 38 patients with recurrent ventricular tachycardia refractory to conventional medications. During the six months of follow-up, encainide prevented the clinical recurrence of ventricular tachycardia in 54 percent

of the treated patients. Although the short follow-up period precludes any definitive conclusions about the efficacy of encainide in this subgroup of patients, the initial results are encouraging.

At UCSF Medical Center, orally given encainide has been used for the treatment of high-frequency PVD's in patients with and without organic heart disease. Preliminary results are now available on the first 10 patients treated. During therapy, nine of the ten patients had virtually complete suppression of PVD's; the PVD frequency during therapy was less than 1 percent of the frequency during placebo. It appears, therefore, that encainide will be as effective in patients with organic heart disease as it has been in patients without such disease. The side effects of encainide have been limited for the most part to the central nervous system, with tinnitus, dizziness and headaches being observed in the reported series.

What is the future of encainide? If side effects remain minor, it may be very useful in suppressing symptomatic PVD's in patients with no organic heart disease. Encainide's role in treating patients with heart disease will require definition and will depend on the results of studies now in progress.

Tocainide

Tocainide, a primary amine analogue of lidocaine, was developed by the Astra Pharmaceutical Company. The addition of the amine side group enables tocainide to avoid the first pass degradation by the liver that orally administered lidocaine undergoes.[17] Basically, tocainide is an orally given lidocaine agent. The electrophysiological properties of tocainide are similar to those of lidocaine and are outlined in Tables 1 and 2.

Tocainide is rapidly and completely absorbed after oral administration. About 40 percent of the drug is excreted unchanged by the kidneys after a single dose, and the remainder is metabolized by the liver. The half-life of tocainide is six to eight hours and therapeutic drug levels in the blood range from 3 to 10 μg per ml. Five studies have evaluated the safety and efficacy of tocainide.[18-22] For the purpose of this review, the results of these studies have been combined. Investigators have noted a correlation between the response of arrhythmias to lidocaine and to orally administered tocainide. Patients responding to intravenous lidocaine therapy usually had a clinical response to orally given tocainide as well, whereas patients who did not respond to lidocaine did not respond to tocainide either. These studies evaluated 78 patients with coronary artery disease and chronic PVD's. After tocainide administration, 50 of the 78 patients had a reduction in PVD frequency of greater than 75 percent. This degree of suppression represented a significant reduction in PVD frequency. The literature also included data on 28 patients treated for symptomatic ventricular tachycardia with tocainide.[20,22] Many of these patients were in the acute phase of myocardial infarctions and, hence, represent a select subgroup of patients with recurrent ventricular tachycardia. When emergency treatment with tocainide was given either intravenously or orally, 15 of 28 patients had suppression of ventricular tachycardia. The follow-up interval of these patients varied from zero to ten months, and recurrences of arrhythmias were infrequent. The obvious limitations of these reports were the small number of patients studied, the limited follow-up and the uncontrolled selection of patients.

One of the main problems with tocainide treatment relates to the drug's side effects. In the clinical series reviewed, 57 percent of patients had minor side effects, which consisted of neurological complaints of tremor, headache, paresthesias, hot flashes or dizziness. Gastrointestinal upset was also frequent. Approximately 10 percent to 15 percent of the treated patients had to discontinue the drug because of intolerable side effects.

What is the future role of tocainide as an antiarrhythmic agent? Tocainide is effective in suppressing PVD's in those patients responsive to intravenous lidocaine therapy. However, treatment will be complicated by a high incidence of side effects, although it may be useful for patients refractory to conventional medications.

Amiodarone

Amiodarone is a benzofuran derivative available in Europe and South America. Although amiodarone will remain an experimental antiarrhythmic agent in the United States long after verapamil, encainide and tocainide are released, it warrants discussion because of its wide use in many referral centers. For example, it is the most commonly used experimental antiarrhythmic drug at the UCSF Medical Center.

The basic electrophysiology of amiodarone is unique because its primary effect is to prolong the transmembrane action potential duration (see Tables 1 and 2).[17] Amiodarone also produces a slight decrease in action potential upstroke velocity without changing automaticity. The clini-

cal electrophysiology of amiodarone consists of a prolongation of the atrial, AV nodal and ventricular refractory periods. In addition, amiodarone prolongs the refractory period of accessory AV pathways (such as Kent bundles and Mahaim fibers).[23] Amiodarone can drastically alter the surface electrocardiogram by producing prolongation of the PR, QRS and QT intervals.

Despite being used clinically for more than 15 years in Europe, little is known about the clinical pharmacology of amiodarone. The drug is 50 percent absorbed after oral administration and is eliminated by unknown mechanisms. A month after discontinuation of long-term amiodarone therapy, tissue levels of the drug have decreased by only 30 percent. Therefore, the half-life of amiodarone is not measured in hours or days but, literally, in weeks. Thus, weeks may be required to attain the desired clinical effect or to eliminate the drug after its discontinuation.

In addition to its antiarrhythmic properties, amiodarone has other physiological effects. It is a noncompetitive antagonist of both α- and β-adrenergic receptors.[17] Amiodarone's antianginal properties are probably related to this β-blocking effect. Despite blocking β-receptors, amiodarone does not usually result in depressed left ventricular function. This seeming paradox is explained by the drug's effect on the peripheral vasculature. Because it antagonizes α-receptors, amiodarone produces a decrease in systemic vascular resistance and reduces left ventricular afterload, thus balancing its β-blocking properties.

The literature contains several studies which evaluate the effectiveness of amiodarone as an antiarrhythmic agent. The largest series was reported by Rosenbaum and co-workers,[24] in which 252 patients with cardiac arrhythmias were studied. Because amiodarone exerts electrophysiological effects in atrial, ventricular and AV nodal tissue, the drug was used to treat a variety of arrhythmic conditions. Rosenbaum studied 30 patients with recurrent atrial fibrillation, atrial flutter, or both. The results of treatment were evaluated using *total* suppression of the arrhythmia as a positive response. During an average follow-up period of 16 months, 29 of 30 patients (97 percent) had a positive response to amiodarone therapy. Rosenbaum administered amiodarone to 59 patients with PSVT and reported that 54 patients (97 percent) had complete suppression of the tachycardia. A third subgroup investigated consisted of 44 patients with recurrent ventricular tachycardia refractory to conventional drugs. Amiodarone resulted in suppression of clinical ventricular tachycardia in 32 of the 44 patients (77 percent). These published results of amiodarone's excellent effectiveness have been substantiated in several smaller series.

At the UCSF Medical Center, amiodarone has been used in the management of both supraventricular and ventricular arrhythmias. The results in patients with atrial fibrillation and PSVT are similar to those reported by Rosenbaum and coworkers.[24] The largest group of patients treated at the medical center has had recurrent ventricular tachycardia, refractory to treatment with conventional drugs. Of 30 such patients treated with amiodarone, 9 patients had a clinical recurrence of ventricular tachycardia during therapy while 21 patients remained asymptomatic. The clinical suppression of ventricular tachycardia in 70 percent of the patients in this high-risk subgroup has been an encouraging finding.

Because amiodarone can be administered once daily, can be taken by patients with depressed left ventricular function, and is therapeutically effective, it would appear to have many characteristics of the ideal antiarrhythmic drug. However, amiodarone treatment can be accompanied by significant side effects (Table 4). For example, in most patients corneal microdeposits will eventually develop during treatment. These microdeposits do not usually interfere with vision and resolve when the patient discontinues the drug. The accumulation of deposits may be alleviated by the frequent use of methycellulose eye drops. Because the amiodarone molecule is 37 percent iodine by weight, thyroid dysfunction can occur. In approximately 1 percent to 3 percent of patients either hyperthyroidism or hypothyroidism will develop. Other side effects include photodermatitis, blueing of the skin when exposed to sunlight, various neurological abnormalities including motor neuropathy, and cerebellar ataxia. In general, the reported side effects of amiodarone resolve when the drug is discontinued.

Amiodarone is an effective multipurpose antiarrhythmic drug that is accompanied by frequent side effects which limit its use to arrhythmias that are refractory to conventional drug treatment.

Electrophysiological Techniques

The newer antiarrhythmic drugs are an important advance in the management of many types of refractory arrhythmias; however, complemen-

tary developments have occurred in the field of invasive electrophysiology as well. Although a comprehensive review is beyond the scope of this report, certain points are relevant to patients with ventricular arrhythmias. First, several investigators have shown that in patients with recurrent ventricular tachycardia, the clinical tachycardia can be reliably reproduced by electrical stimulation of the right ventricle without significant morbidity or mortality.[25,26] In addition, several studies have shown that failure in the cardiac catheterization laboratory to stimulate the tachycardia after drug administration is predictive of suppression of the arrhythmia during long-term therapy.[25,27] Thus, physicians now have a realtively safe and rapid means by which to assess the efficacy of antiarrhythmic therapy in patients with life-threatening ventricular arrhythmias. At present, these invasive techniques are used at the UCSF Medical Center to evaluate therapy in all patients with sustained ventricular tachycardia or aborted sudden death syndrome.

Conclusion

There will soon be available many newer antiarrhythmic drugs, each with its own advantages and side effects. Use of these drugs should be governed by a careful assessment of each drug's risk-benefit ratio for a particular patient. In this way, the care and quality-of-life of patients with arrhythmias can be much improved.

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